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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/417,226	Applicant(s) SUNDREHAGEN ET AL	
	Examiner Ja-Na A Hines	Art Unit 1645	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9-12,16-20,24-33,35,36,42-44 and 47-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,9-12,16-20,24-33,35,36,42-44 and 47-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Application/Control Number: 09/417,226
Art Unit: 1645

DETAILED ACTION

Amendment Entry

1. The amendment filed December 10, 2001 was entered. Claim 1 was amended. Claims 1, 3-7, 9-12, 16-20, 24-33, 35-36, 42-44, 47-50 are under consideration in this office action.

Withdrawal of Rejections

2. The following rejections have been withdrawn in view of applicant's amendments and arguments:

a) The rejection of claims 1, 5-7, 10, 12, 16-20, 26, 42-44, 47-48 and 50 under 35 U.S.C. 103(a) as being patentable over McLean et al., in view of Houts;
b) The rejection of claims 9, 11, 24-25 and 35-36 under 35 U.S.C. 103(a) as being patentable over McLean et al., in view of Houts in further view of Herbert et al;
c) The rejection of claims 4 and 49 under 35 U.S.C. 103(a) as being patentable over McLean et al., in view of Houts in further view of Allen; and
d) The rejection of claims 27-33 under 35 U.S.C. 103(a) as being patentable over McLean et al., in view of Houts in further view of Hoyle.

Response to Arguments

3. Applicant's arguments filed January 29, 2001 have been fully considered but they are not persuasive.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 3-7, 9-12, 16-20, 24-33, 35-36, 42-44, 47-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained. Claim 1 was rejected as being vague and indefinite because the preamble

of claim 1 recites an assay method for the determination of transcobalamin II bound cobalamin in a body sample, however the detection step states that the cobalamin content in said cobalamin containing liquid will be determined. The claim was unclear as to whether the released cobalamin concentration is being assayed or if the cobalamin bound by TC II is being assayed.

Applicant argues that "transcobalamin II bound cobalamin" term is equivalent to the measurement of "cobalamin content" in the final line. However, if the cobalamin content is equivalent to the transcobalamin II bound cobalamin, then consistent terminology should be used throughout the claims.

Applicant urges that the claims do not lack a correlation step that correlates the determination of holo-transcobalamin II (holo-TCII) and determining the cobalamin content by measuring the cobalamin or the TCII –protein content arising from the holo-TCII released from the specific binding ligand. Currently the claim's final step measures cobalamin which was released into the liquid sample, not cobalamin bound to transcobalamin (holo-TCII) as the preamble of the claim recites. Applicant must positively recite necessary method steps. Stating that a measurement of cobalamin or TCII protein arising from the holo-TCLL released from the specific binding ligand is not a sufficiently positively recited method step. Thus the rejection is maintained.

New Grounds for Rejection
Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3-7, 9-12, 16-20, 24-33, 35-36, 42-44 and 47-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 contains new matter. There is no support for the amendment reciting a volume of liquid which is at least 3 times less than the volume of said cell free sample. The specification fails to disclose that the volume of liquid is at least 3 times less then the volume of the sample. Applicant has failed to cite page and line number support for the amendment. It appears that there is no teaching of the recited limitation, and the amendment contains new matter, therefore it is rejected.

6. Claims 1, 3-7, 9-12, 16-20, 24-33, 35-36, 42-44 and 47-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific binding ligands which bind TC II such as an anti-TC II antibody or anti-TC antibody fragment, does not reasonably provide enablement for a specific binding ligand such as polypeptides, oligopeptide, small organic chemical, binders from combinatorial chemistry libraries or phage display library or specifically binding sequences of DNA and RNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In particular, claims 1,5 and 26 broadly recite specific binding ligands, however only anti-TC II antibodies are enabled by the specification.

The specification does not teach making specific binding ligands such as like polypeptide, oligopeptide, small organic chemical, binders from combinatorial chemistry libraries or phage display library or specifically binding sequences of DNA and RNA that only bind to TCII. For instance, there is no disclosure of peptides, small organic chemicals or sequences that preferentially bind TC II. Absent factual evidence that the recited ligands will bind TC II; it is not deemed reasonable that one skilled in the art would know how the claimed ligands would bind to TC II. The specification broadly recites a range of binding ligands without any specificity to TCII, when the suspension is used for targeting selected cells or tissues the microdevices should contain molecules effective to bind the markers carried on the surface of the target cells (page 8 para. 3). It is known that monoclonal antibodies and associated antibody fragments directed to epitopes on TCII can act as specific binding ligands. However, there is no evidence that the specific binding ligands such as polypeptides, oligopeptide, small organic chemical, binders from combinatorial chemistry libraries or phage display library or specifically binding sequences of DNA and RNA without any specific binding regions specific to TC II have been identified and further, will perform in the assay. Without the specific binding ligands, the effects of ligands ability to select TCII is largely unpredictable. Therefore the recitation of a specific binding ligand without specific regions or sequences directed specifically to TCII will result in an unpredictable use and therefore unreliable correspondence between the broadly claimed specific binding ligands and the indicated anti-TC II antibodies disclosed in the specification with known specific binding

affinity to TCIL; therefore the claimed specific binding ligands lack support regarding utility and/or enablement.

Absent clear demonstration of the production of specific binding ligands such as polypeptides, oligopeptide, small organic chemical, binders from combinatorial chemistry libraries or phage display library or specifically binding sequences of DNA and RNA which specifically and preferentially bind TC II, the recited specific binding ligands could not be used in any manner for the determination of holo-TC II in a body sample comprising the recited steps. In absence of further guidance from Applicants, the skilled artisan would have to discover to specific binding regions for each and every named specific binding ligand. Such experimentation requires ingenuity beyond that expected of one of ordinary skill in the art. Thus non-routine experimentation demonstrates that the specification is not enabled for specifically binding ligands. Therefore, one skilled in the art could not make and/or use the invention as claimed.

7. Claims 1, 3-7, 9-12, 16-20, 24-33, 35-36, 42-44, 47-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the term TCII-protein content, however, the is no definition of what the TCII protein content is referring too. If TCII protein is equivalent to another protein, then consistent terminology should be used throughout the claim. The claim is vague in its reference to TCII-protein content, thus it is unclear whether TCII protein content is

measuring TCII or some other transcobalamin protein. Therefore, the claim is rejected as being vague and indefinite.

8. Claims 16-20 and 25 are unclear. Claims 16-17 and 25 are drawn to a preliminary separation step, however the claims do not recite when this preliminary separation step will occur. It is unclear if the preliminary step occurs before adding cobalamin to the sample or at some other time. Thus the claim is vague because it does not say what the preliminary step is preliminary too.

9. Claims 16 and 19 recite the use of apo-forms of TCII and HC, however it is unclear whether the apo forms are comprised within the sample or added to the sample. Thus the claims are unclear.

10. Claim 19 is unclear. The claim recites adding cobalamin to the assay to increase the amount bound thus increasing the amount present, however this process is unclear. The meets and bounds of the claim are unclear as to what steps the claims are directed too. Thus the claim is unclear and applicant is asked to clarify the claim.

11. Claim 24 is unclear with respect to what fraction is separated from what sample.

12. Claim 25 is inconsistent. The claim recites that the fraction is at least 80% free however that is inconsistent with what free means. It is unclear as to whether if there is no TC II or if there is some TC II present.

13. Claims 35 and 36 are unclear. It is unclear how the concentration of the lignad is determined. For instance, is there an addition of a binding ligand in solution that would dilute the TC II or holo-TCII or is the binding ligand is immobilized, and then this is a measure of concentration on the surface. Thus the claims are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 5, 7, 9, 11, 12, 42-44, 47, 48 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Herbert et al., US Patent 4,680,273.

Herbert et al., teach a method of selectively freeing from transcobalamin II (TCII) and determining the amount vitamin B_{12} or cobalamin in a sample. Holo transcobalamin II is equivalent to TCII containing bound vitamin B_{12} (col. 2 lines 29-31). The cobalamin which is carried by TCII may be determined by providing a blood sample which contains essentially only TCII that has been separated from other serum proteins and determining the cobalamin content (col. 3 lines 3-6). Separation steps taught include precipitation of TCII, although other methods for separating TCII from a sample are applicable (col. 3 lines 40-46). TCII can be separated from a sample using selective antibodies (col. 3 lines 54-55) where the antibody can be coupled to a solid support to more easily separate TCII (col. 3 lines 63-64). At pH=6, TCII binds to sephadex while the other transcobalamin proteins do not (col.3 line 65). Once the TCII-Vitamin B_{12} solution is obtained, the resulting solution may be subjected an assay for vitamin B_{12} where radioassay for vitamin B_{12} includes the removal of vitamin B_{12} from TCII complex, for example by heating or the use of hydrochloric acid at pH=2 to destroy the TCII and removal of the B_{12} (col. 4 lines 15-20). Vitamin B_{12} dissociates from TCII when both the

ionic strength and pH are low (col. 4 lines 35-37). Thus cobalamin can be selectively freed from TCII (col. 4 lines 25-26). The assay for vitamin B_{12} is accomplished by using a binder specific for cobalamins (col. 5 lines 10-15). In an immunoassay the binder can be a monoclonal or polyclonal antibody, a tracer is also used which can be vitamin B_{12} or an appropriate analog that is labeled with a detectable marker (col. 5 lines 16-30). The binder can be in either supported or unsupported form, and in the instances where the binder is supported, it can be supported by a solid support and the bound free fractions may be separated without the use of a separating agent, while if the binder is unsupported, then the bound free fractions can be separated by using a separating agent (col. 5 lines 33-42). Finally, in one type of assay an amount of tracer and any vitamin B_{12} present in a sample can compete for a limited number of binding sites on the binder and the amount of tracer becomes inversely proportional to the amount of vitamin B_{12} in the sample (col. 5 lines 29-34). Binding of additionally haptocorrins such as transcobalamin I and III are also taught, along with methods of separation and detection (col. 3-4). Therefore, Herbert et al., teach an assay method for the determination of holo-transcobalamin II in a body sample comprising the recited steps.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 3,16,17, 24-26 and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herbert et al., US Patent 4,680,273 in view of Houts et al., US Patent 4,465,775. However, Herbert et al, does not teach a fraction separation step as disclosed by the claims.

Houts teaches a method of assaying vitamin B_{12} based on competitive binding which employs a labeled reactant which carries a group which can be readily identified (col. 1 lines 17-20). Commonly used labels are radioactive atoms and fluorescent or enzyme groups (col. 1 lines 21-22). Also, competitive binding assays use proteins which not only bind to B_{12} , but also to cobalamin analogues including transcobalamin II, R proteins and intrinsic factor (IF) present in human sera (col. 1 lines 55-66). Houts teaches a comparison of cyanocobalamin and cyanocobalamin-d-iodohistamide in a competitive protein binding assay (col. 5 lines 3-6). The tracers (cyanocobalamin and cyanocobalamin-d-iodohistamide) were diluted in a KCN mixture (col.5 line 13). A centrifugation step was performed on the supernates and the tubes were decanted and counted (col. 5 lines 19-21). The binding proteins can be IF or a mixture of IF and R-protein (col. 5 lines 25-30). The assay also uses sample from human serum or plasma.

No more then routine skill is involved in adjusting the amount of a component of a claimed process as stated in the claims. The cited references teach a separation step and steps that release to previously bound cobalamin into a concentrated environment. Therefore, neither changes in concentrations nor determining optimum concentrations which are suitable for materials have been held to involve patentable inventions.

Therefore, it would have been obvious at the time of applicants invention to use the antibodies to transcobalamin II in a competitive sandwich ELISA assay on a solid support as taught by Houts, in the method of determining the cobalamin content in a sample as taught by Herbert , because Houts teaches a modified method of assaying TCII or any cobalamin analogues using samples from human plasma or serum, where a centrifuge step is performed and cyanocobalamin in either a direct or indirect assay can be assayed with any one of a variety of detectable signals that can indicate presence using immobilized and non-immobilized ligands.

16. Claims 6-7, 12, and 8-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herbert et al., and Houts as applied to claims 1,5 and 16 above further in view of McLean et al.

Herbert et al., and Houts have been discussed above, however neither teach a monoclonal antibody specific for both apo and holo transcobalamin. McLean et al., teach several monoclonal antibodies to transcobalamin II (TCII). Three types of monoclonal antibody have been characterized, wherein Type 3 can be used to immunoprecipitate TCII (page 237 para. 4). A sandwich-enzyme linked immunosorbant assay analysis of monoclonal antibody binding to TCII was performed (page 236 para. 4). The ELISA plates were coated with anti-TCII monoclonal antibodies, immobilized and found capable of binding to both or either holo-TCII and apo-TCII and show specific or preferential binding ability (table 1). The authors used biotinylated anti-TCII monoclonal antibody and added streptavidin-peroxidase as a means of detection (page

236 para. 4). The immobilized antibodies were used to capture TCII and then detected using biotinylated monoclonal antibodies, further when the biotinylated antibody used for detection binds to an epitope overlapping with plate bound antibody used to capture TCII (page 240 para. 1). Free cyanocobalamin was obtained from Sigma Chemical (page 235 para. 4) and tested using the monoclonal antibodies in the presence and absence of the apo-TCII receptor (page 239 para. 1). The antibodies generated can also be used to immunoprecipitate TCII in bovine serum (page 237 para. 5).

Therefore one skilled in the art would have expected a reasonable level of success by including monoclonal antibodies specific for apo and holo transcobalamin and known to be associated with biotin and avidin as taught by McLean et al., with the assay methods for the determination of TCII bound cobalamin sample comprising contacting a sample body fluid with an immobilized specific binding ligand like a antibody specific for TCII, separating the bound fraction from the unbound fraction and measuring the amount of TCII bound cobalamin obtained as taught by Herbert et al., in view of Houts because McLean et al., teach that no more then routine skill is required to incorporate a monoclonal antibody specific for the apo or holo TCII ligand which can detect or immunoprecipitate TCII in serum.

17. Claims 4 and 49 rejected under 35 U.S.C. 103(a) as being unpatentable over Herbert et al., in view of Houts and further in view of Allen et al., (US Patent 5,374,560). Herbert et al., and Houts have been discussed above however neither teach an assay amenable to automation. Allen et al., (US Patent 5,374,560) teaches a method of diagnosing cobalamin deficiency in humans by measuring serum levels (col. 1 lines 13-

16). The method screens cobalamin deficiency using serum, urine, cerebral spinal fluid, or plasma and the assay may be provided in a kit or can be used in an automated process.

Therefore, it would have been obvious to automate the method as taught by Allen e al., in the method of determination as taught by Herbert et al., in view of Houts, because Allen et al., shows it to be conventional and well known to automate assays to detect cobalamin. Furthermore, it has been held that broadly providing a mechanical or automatic assay to replace manual activity which has accomplished the same results involves only routine skill in the art (*In re Venner,* 120 USPQ 192).

18. Claims 27-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herbert et al., and McLean et al, as applied to claims 1 above further in view of Hoyle et al. Herbert et al., and McLean have been discussed above, however neither teach the specific affinity constants recited in claims 27-33.

Hoyle et al., (US Patent 5,451,508) using specific monoclonal antibodies having high affinity constants use in all immunoassays since they are known in the art to increase sensitivity of the immunoassay. Hoyle et al., teach the use of monoclonal antibodies with affinity constants of at least 5×10^{9} Mol^{-1}, and most preferably 5×10^{10} Mol^{-1}, wherein monoclonal antibodies can be used as complete antibodies, chimeric antibodies or bivalent fragments (col. 2-3 lines 64-10). Figure 2 shows more sensitive antigen determination was achieved with monoclonal antibodies.

The monoclonal antibodies taught by McLean et al., have the affinity constants required by claims 27-33. The affinity properties as recited by the claims are conventional affinities for monoclonal antibodies. Thus, one of skill in the art would desire a high affinity antibody to increase sensitivity of the assay. Furthermore, Applicants state in the specification, page 9 paragraph 2, that suitable antibodies for use as binding ligands in the present invention are disclosed by McLean et al.

Therefore, no more then routine skill would have been required to incorporate monoclonal antibodies of McLean et al, with high affinity constants as taught by Hoyle et al., into the assay of Herbert et al., because Hoyle et al., teach it would have been obvious at the time of applicants invention to use antibodies with the high affinity constants because they provide for a more sensitive immunoassay.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines
March 12, 2002

PATRICIA A. DUFFY
PRIMARY EXAMINER